Annals of Internal Medicine®

In the Clinic®

Chronic Kidney Disease

Nearly 14% of Americans have chronic kidney disease (CKD), which includes persistent decrements in glomerular filtration rate or the presence of albuminuria. Although CKD is commonly attributed to diabetes or hypertension, there is growing awareness of the interplay among cardiovascular, kidney, and metabolic health. Progression of CKD can result in metabolic abnormalities and end-stage kidney disease, but cardiovascular events are even more common. The main goals of CKD treatment include slowing the decline in kidney function, preventing cardiovascular disease, and treating metabolic complications. Recent pharmacologic advancements have yielded effective therapeutic agents capable of concurrently addressing all of these objectives.

Screening and Prevention

Diagnosis

Treatment

CME/MOC activity available at Annals.org.

Physician Writers
Morgan E. Grams, MD, PhD
Michal L. Melamed, MD, MHS
NYU Grossman School of Medicine, New York, New York (M.E.G., M.L.M.)

doi:10.7326/ANNALS-25-02684

This article was published at Annals.org on 9 September 2025.

CME Objective: To review current evidence on screening, prevention, diagnosis, and treatment of chronic kidney disease.

Funding Source: American College of Physicians.

Acknowledgment: The authors thank Paul Drawz, MD, MHS, MS, and Mahboob Rahman, MD, MS, authors of the previous version of this In the Clinic.

Disclosures: All relevant financial relationships have been mitigated. Disclosure forms are available with the article online.

With the assistance of additional physician writers, the editors of *Annals of Internal Medicine* develop In the Clinic using MKSAP and other resources of the American College of Physicians.

In the Clinic does not necessarily represent official ACP clinical policy. For ACP clinical guidelines, please go to www.acponline.org/clinical_information/guidelines.

© 2025 American College of Physicians

ACP American College of Physicians®
Leading Internal Medicine, Improving Lives

Downloaded from https://annals.org by Universidad Nacional Autonoma on 09/12/2025.

SHOUT
SHARE
IT

1. United States Renal Data System. 2023 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. National Institute of Diabetes and Digestive and Kidney Diseases; 2023.
2. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2024;105:S117-S314. [PMID: 38490803]
3. American Diabetes Association Professional Practice Committee. 11. Chronic kidney disease and risk management: Standards of Care in Diabetes–2024. Diabetes Care. 2023;47:S219-S230. [PMID: 38078574]
4. National Institute for Health and Care Excellence. Chronic kidney disease: assessment and management. NICE guideline NG203. Updated 24 November 2021. Accessed at www.nice.org.uk/guidance/ng203 on 2 January 2025.
5. McEvoy JW, McCarthy CP, Bruno RM, et al; ESC Scientific Document Group. 2024 ESC guidelines for the management of elevated blood pressure and hypertension. Eur Heart J. 2024;45:3912-4018. [PMID: 39210715]

Screening and Prevention

Which patients are at increased risk for chronic kidney disease?

The most common cause of chronic kidney disease (CKD) in the United States is diabetes (1). Table 1 shows other risk factors for CKD, including hypertension, cardiovascular disease, obesity, and older age (2).

Should clinicians screen patients for CKD?

The U.S. Preventive Services Task Force is updating a recommendation statement on screening in the general population. The international guideline organization Kidney Disease: Improving Global Outcomes (KDIGO) strongly recommends screening adults at risk for CKD, including people with hypertension, diabetes, or cardiovascular disease (2). The KDIGO guidance concurs with that issued by other societies, such as the American Diabetes Association (ADA), the U.K. National Institute for Health and Care Excellence (NICE), the European Society of Hypertension (ESH), and the European Society of Cardiology (ESC) (3–5). The recommendations are supported by an older cost-effectiveness study among people with hypertension and diabetes (6). A more recent study that incorporated the effectiveness of sodium–glucose cotransporter-2 (SGLT-2) inhibitors on CKD progression alone suggested that broader population-based screening may also be cost-effective (7).

How and how often should patients be screened for CKD?

Initial screening should test for glomerular filtration rate (GFR); albuminuria; and, if indicated, other markers of kidney damage. GFR is most commonly assessed using serum creatinine and converted to estimated GFR (eGFR) using the CKD-EPI 2021 equation, which contains additional terms for age and sex (8). However, creatinine is affected by factors unrelated to GFR, including muscle mass. For patients in whom accurate GFR estimation is paramount as well as those with extreme

Table 1. **Risk Factors for CKD***

Domains	*Examples*
Common risk factors	Diabetes Cardiovascular disease (including heart failure) Hypertension Prior acute kidney injury
Residence in geographic areas with high prevalence of CKD	Areas with endemic CKD of undetermined origin Areas with high prevalence of *APOL1* genetic variants Environmental exposures Social determinants of health
Genitourinary disorders	Structural urinary tract disease Recurrent kidney calculi
Multisystem diseases/chronic inflammatory conditions	Systemic lupus erythematosus Vasculitis HIV Hepatitis B or C
Iatrogenic (related to drug treatments and procedures)	Drug-induced nephrotoxicity and radiation nephritis
Family history or known genetic variant associated with CKD	Polycystic kidney disease *APOL1*-associated kidney disease Type IV collagen disorders Medullary cystic kidney disease
Risk factors related to pregnancy and birth	Preterm birth Small for gestational age Preeclampsia/eclampsia
Environmental exposures that promote CKD risk	Cadmium, lead, and mercury exposure Polycyclic hydrocarbons Pesticides

CKD = chronic kidney disease.
** Adapted from reference 2.*

Downloaded from https://annals.org by Universidad Nacional Autonoma on 09/12/2025.

values of muscle mass, clinicians may also test serum cystatin C. Albuminuria should be estimated using an albumin–creatinine ratio (ACR) from a spot urine sample. Because of diurnal variation, the most accurate estimate comes from a first morning void, but a random sample is also acceptable. Patients with type 2 diabetes should be screened for CKD at the time of diagnosis and then annually; patients with type 1 diabetes are recommended for annual screening starting at 5 years after initial diagnosis (3).

Are preventive measures useful for patients at increased risk for CKD?

In patients with diabetes, good glycemic control reduces risk for CKD. Patients can also benefit from dietary and lifestyle interventions (3).

In patients with obesity, data suggest that weight loss can prevent CKD. Trial evidence suggests glucagon-like peptide-1 receptor agonists (GLP-1RAs) prevent onset of urine ACR above 300 mg/g, and observational studies suggest bariatric surgery is associated with a slower decrease in eGFR (9, 10).

In patients with hypertension, the American Heart Association (AHA) and the ESC recommend maintaining blood pressure below 130/80 mm Hg through lifestyle modification and antihypertensive drug therapy (5, 11). Treating hypertension reduces risk for cardiovascular events and all-cause mortality (12). The AHA recommends focusing on "Life's Essential 8," which address diet, physical activity, nicotine exposure, sleep health, body mass index, blood lipids, blood glucose, and blood pressure (13).

The SPRINT trial randomly assigned 9361 adults with hypertension to an intensive blood pressure target (systolic blood pressure <120 mm Hg) or a standard target (systolic blood pressure <140 mm Hg). The trial was stopped early due to a lower rate of the primary composite cardiovascular outcome in the intensive treatment group (hazard ratio [HR], 0.75 [95% CI, 0.60 to 0.90]; P = 0.003) (12). The intensive treatment group had a steeper decrease in eGFR during the trial period, but these findings did not persist in long-term follow-up, providing some reassurance about the kidney safety of this approach (14).

The Look AHEAD trial randomly assigned 5145 patients with type 2 diabetes and obesity or overweight to an intensive lifestyle intervention that promoted weight loss through diet and exercise or to a control group that received diabetes support and education. Although there was no significant difference in the primary composite outcome of death due to cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina, subsequent studies showed a reduction in the incidence of very-high-risk CKD in the intensive intervention group (HR, 0.69 [CI, 0.55 to 0.87]; P = 0.0016) (15, 16).

In the SELECT trial, 17 604 participants with cardiovascular disease (prior myocardial infarction, stroke, or symptomatic peripheral artery disease) and a body mass index of 27 kg/m^2 or higher were randomly assigned to semaglutide, 2.4 mg, or placebo. Overall, a 5-component kidney composite outcome (death due to kidney disease, initiation of chronic kidney replacement therapy, onset of persistent eGFR <15 mL/min/1.73 m^2, persistent reduction in eGFR by ≥50%, or onset of urine ACR >300 mg/g) occurred in 2.2% of participants in the placebo group and 1.8% of those in the semaglutide group (P = 0.02). The risk reduction was similar among participants with eGFR of 60 mL/min/1.73 m^2 or higher (10).

6. Komenda P, Ferguson TW, Macdonald K, et al. Cost-effectiveness of primary screening for CKD: a systematic review. Am J Kidney Dis. 2014;63:789-797. [PMID: 24529536]
7. Cusick MM, Tisdale RL, Chertow GM, et al. Population-wide screening for chronic kidney disease: a cost-effectiveness analysis. Ann Intern Med. 2023;176:788-797. [PMID: 37216661]
8. Inker LA, Eneanya ND, Coresh J, et al; Chronic Kidney Disease Epidemiology Collaboration. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med. 2021;385:1737-1749. [PMID: 34554658]
9. Chang AR, Chen Y, Still C, et al. Bariatric surgery is associated with improvement in kidney outcomes. Kidney Int. 2016;90:164-171. [PMID: 27181999]
10. Colhoun HM, Lingvay I, Brown PM, et al. Long-term kidney outcomes of semaglutide in obesity and cardiovascular disease in the SELECT trial. Nat Med. 2024;30:2058-2066. [PMID: 38796653]
11. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71:e13-e115. [PMID: 29133356]
12. Wright JT Jr, Williamson JD, Whelton PK, et al; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373:2103-2116. [PMID: 26551272]
13. Lloyd-Jones DM, Allen NB, Anderson CAM, et al; American Heart Association. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. Circulation. 2022;146:e18-e43. [PMID: 35766027]
14. Drawz PE, Lenoir KM, Rai NK, et al. Effect of intensive blood pressure control on kidney outcomes: long-term electronic health record–based post-trial follow-up of SPRINT. Clin J Am Soc Nephrol. 2024;19:213-223. [PMID: 37883184]

 © 2025 American College of Physicians

Downloaded from https://annals.org by Universidad Nacional Autonoma on 09/12/2025.

Screening and Prevention... Recommendations differ on the utility of screening patients for CKD. However, guidelines that recommend against screening precede key clinical trials establishing the efficacy of drug classes such as SGLT-2 inhibitors and GLP-1RAs in preventing CKD complications. Given the centrality of eGFR in drug dosing decisions and the availability of therapy for patients with albuminuria, we recommend screening patients who are at risk for CKD with serum creatinine, cystatin C if available, and urine ACR. This includes annual screening in patients with diabetes and, more controversially, in patients with hypertension, patients with cardiovascular disease, and older patients.

CLINICAL BOTTOM LINE

Diagnosis

What is the definition of CKD?

The 2024 KDIGO guidelines define CKD as GFR below 60 mL/min/1.73 m^2, urine ACR above 30 mg/g, or presence of other markers of kidney damage for more than 3 months (2). Kidney damage includes functional abnormalities of the kidneys (for example, abnormalities of the urinary sediment, such as dysmorphic erythrocytes) and structural abnormalities as noted on imaging studies. CKD can be diagnosed on initial presentation if additional stigmata of chronic disease are present, such as previous values of decreased GFR or albuminuria on qualitative urine dipstick or quantitative assessment, markers of chronicity on imaging or histology, or history of a disease that commonly causes or contributes to CKD.

If the KDIGO definition is applied to data from the National Health and Nutrition Examination Survey, more than 31 million U.S. adults have CKD (1). From 2005 to 2020, the prevalence of the disease increased by 12% according to estimates from the U.S. Renal Data System.

How should clinicians stage CKD?

The recommended method for estimating GFR in the United States is the CKD-EPI 2021 equation (8, 17). This equation does not use race as an input variable, unlike earlier estimating equations (18). There are CKD-EPI equations for GFR based on creatinine alone (eGFRcr), cystatin C alone (eGFRcys), or both (eGFRcr-cys). eGFRcr-cys is the most accurate method of assessing GFR in the majority of settings (19, 20). Most clinicians use eGFRcr as the initial screening test, but if a patient is discovered to have eGFRcr below 60 mL/min/1.73 m^2, KDIGO guidelines recommend checking serum cystatin C for a more accurate estimate of GFR (eGFRcr-cys) for CKD staging (2). Stage of CKD is classified using a patient's eGFR and urine ACR (**Figure 1**).

The third aspect of CKD staging, cause of CKD, can be more difficult to assign and frequently requires a kidney biopsy (2).

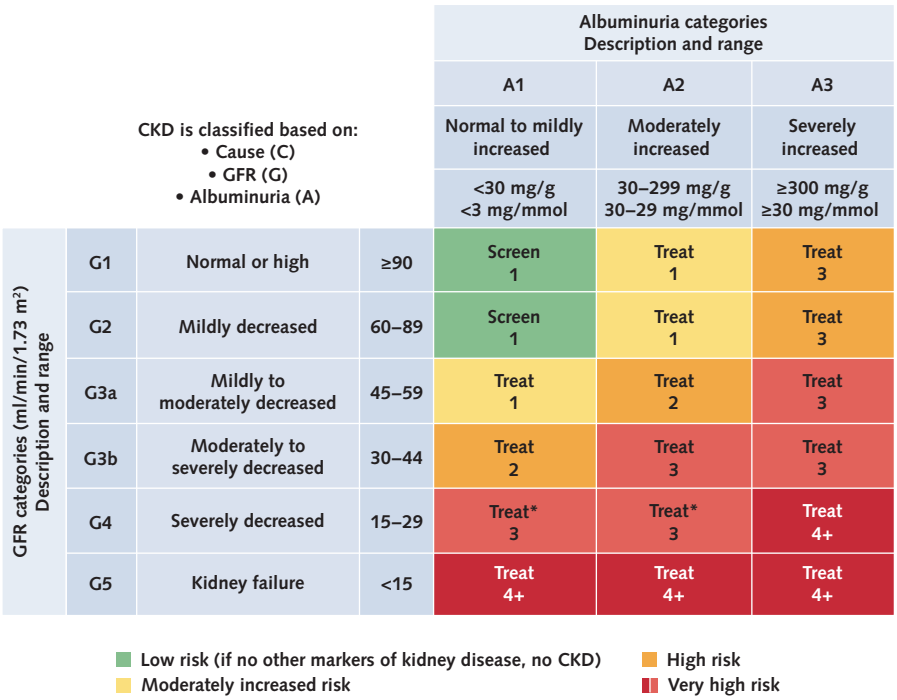
What clinical manifestations might provide clues about the cause of CKD?

A careful medical history and physical examination can provide clues about the cause of CKD. Patients with long-standing, poorly controlled diabetes may be more likely to have diabetic nephropathy. However, in the National Institutes of Health–sponsored Kidney Precision Medicine Project (KPMP), only 58% of those with diabetes and kidney disease had diabetic nephropathy on kidney biopsy (www.kpmp.org). Similarly, patients with long-standing hypertension with hypertensive retinopathy are likely to have hypertensive changes on biopsy (63% in the KPMP data) (21). It is worth noting that the presence of hypertension or diabetes

15. Wing RR, Bolin P, Brancati FL, et al; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med.. 2013;369:145-154. [PMID: 23796131]
16. Look AHEAD Research Group. Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a secondary analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol. 2014;2:801-809. [PMID: 25127483]
17. Delgado C, Baweja M, Crews DC, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. Am J Kidney Dis. 2022;79:268-288.e1. [PMID: 34563581]
18. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-612. [PMID: 19414839]
19. Fu EL, Levey AS, Coresh J, et al. Accuracy of GFR estimating equations based on creatinine, cystatin C or both in routine care. Nephrol Dial Transplant. 2024;39:694-706. [PMID: 37813817]
20. Pottel H, Björk J, Rule AD, et al. Cystatin C-based equation to estimate GFR without the inclusion of race and sex. N Engl J Med. 2023;388:333-343. [PMID: 36720134]
21. Fogo A, Breyer JA, Smith MC, et al. Accuracy of the diagnosis of hypertensive nephrosclerosis in African Americans: a report from the African American Study of Kidney Disease (AASK) trial. AASK Pilot Study Investigators. Kidney Int. 1997;51:244-252. [PMID: 8995739]

Downloaded from https://annals.org by Universidad Nacional Autonoma on 09/12/2025.

Figure 1. **Frequency of monitoring glomerular filtration rate (GFR) and albuminuria in people with chronic kidney disease (CKD).**


CKD is classified based on:
• Cause (C)
• GFR (G)
• Albuminuria (A)
Albuminuria categories
Description and range
A1
Normal to mildly increased
<30 mg/g
<3 mg/mmol
A2
Moderately increased
30–299 mg/g
30–29 mg/mmol
A3
Severely increased
≥300 mg/g
≥30 mg/mmol
GFR categories (ml/min/1.73 m²)
Description and range
G1 Normal or high ≥90
Screen 1 | Treat 1 | Treat 3
G2 Mildly decreased 60–89
Screen 1 | Treat 1 | Treat 3
G3a Mildly to moderately decreased 45–59
Treat 1 | Treat 2 | Treat 3
G3b Moderately to severely decreased 30–44
Treat 2 | Treat 3 | Treat 3
G4 Severely decreased 15–29
Treat* 3 | Treat* 3 | Treat 4+
G5 Kidney failure <15
Treat 4+ | Treat 4+ | Treat 4+
Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

Albuminuria and GFR grid reflects the risk of progression by intensity of coloring (green, yellow, orange, red, and deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year). Reproduced from American Diabetes Association, Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO), 2022. Copyright and all rights reserved. Material from this publication has been used with the permission of the American Diabetes Association.

does not rule out another cause of CKD, and hypertension is a common consequence of CKD.

Other clues to the cause of CKD may be revealed through a comprehensive history. For example, a history of heart failure or cirrhosis might suggest decreased perfusion and effective intravascular volume or kidney injury from inflammation and activation of the sympathetic and renin–angiotensin–aldosterone systems (22, 23). Infection with syphilis, hepatitis B or C virus, or HIV may cause glomerular disease, so clinicians should ask all patients about intravenous drug use and high-risk sexual behavior. A family history of kidney disease may be a clue to diagnosis of *APOL1* kidney disease, polycystic kidney disease, type IV collagen disorders, or medullary cystic kidney disease (24). Urinary frequency, hesitancy, incontinence, nocturia, or dysuria may reflect underlying urinary tract disease, such as obstruction or infection. It is important to note that nocturia is also a frequent symptom of advanced CKD. Rash, arthritis, mononeuropathy, or other systemic symptoms may suggest vasculitis or systemic lupus erythematosus. Clinicians should ask about "bubbly" or "foamy" urine, which indicates albuminuria; weight gain and peripheral edema, which could signify nephrotic syndrome; and hematuria, which could indicate glomerulonephritis. Recent diarrhea, bleeding, and dehydration may cause acute kidney injury, which predisposes to CKD (25).

Physical examination should include measuring blood pressure, checking for orthostasis in patients with recent fluid loss, examining the skin for rashes and petechiae, and examining the fundus for diabetic retinopathy (microaneurysms, dot hemorrhages, and cotton wool spots) or hypertensive retinopathy

22. Velez JCQ, Therapondos G, Juncos LA. Reappraising the spectrum of AKI and hepatorenal syndrome in patients with cirrhosis. Nat Rev Nephrol. 2020;16:137-155. [PMID: 31723234]
23. Braam B, Joles JA, Danishwar AH, et al. Cardiorenal syndrome–current understanding and future perspectives. Nat Rev Nephrol. 2014;10:48-55. [PMID: 24247284]
24. Köttgen A, Cornec-Le Gall E, Halbritter J, et al. Genetics in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2022;101:1126-1141. [PMID: 35460632]
25. Chawla LS, Eggers PW, Star RA, et al. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med. 2014;371:58-66. [PMID: 24988558]

 © 2025 American College of Physicians

Downloaded from https://annals.org by Universidad Nacional Autonoma on 09/12/2025.

(atrioventricular nicking, silver wiring, tortuosity, hemorrhages, exudates, and papilledema). The physician should evaluate for heart failure by looking for pulmonary rales, jugular venous distention, an S3, and peripheral edema. A renal bruit suggests renal artery stenosis, and inflamed joints can suggest vasculitis or autoimmune processes. Stigmata of liver disease, including jaundice, ascites, and spider angiomas, may suggest hepatorenal syndrome. Asterixis, encephalopathy, and the presence of a pericardial friction rub may indicate uremia and the need for prompt initiation of dialysis.

What laboratory tests and imaging studies should be done?

The laboratory work-up should be tailored to the stage and potential cause of CKD. To start, a complete blood count, comprehensive metabolic panel, urinalysis, urine ACR (sometimes referred to as urine microalbumin), and lipid panel should be tested. If eGFRcr is below 60 mL/min/1.73 m^2; the patient has extremes of muscle mass, liver disease, cancer, or heart failure; or the patient requires medications that require dose adjustment in the setting of lower GFR, the KDIGO guideline recommends also measuring cystatin C (2). Cystatin C is increasingly available as a test within hospital systems and is widely available as a send-out test to the major laboratories. As previously mentioned, the combined equation (eGFRcr-cys) most accurately estimates kidney filtration in most clinical settings. Although urine ACR is the gold standard for classifying patients into CKD stages, if nonalbumin proteinuria (for example, multiple myeloma) is suspected or the value is above the laboratory threshold for reporting, a urine protein–creatinine ratio should also be checked. In patients with GFR below 60 mL/min/1.73 m^2, serum phosphorus and intact parathyroid hormone (PTH) levels should be measured and renal ultrasonography should be performed as a baseline screening tool to look for hydronephrosis, cysts, and stones and to assess echogenicity, size, and symmetry of the kidneys. Finally, if suggested by the medical history, physical examination, and urine studies, additional blood work can be pursued, such as antinuclear antibodies for systemic lupus erythematosus; serum antineutrophil cytoplasmic antibodies for vasculitis; anti–glomerular basement membrane (GBM) antibodies for anti-GBM disease; phospholipase A2 (PLA2) receptor and thrombospondin type-1 domain-containing 7A (THSD7A) antibodies for membranous nephropathy; testing for exposures to hepatitis B and C viruses, syphilis, and HIV; and serum and urine protein immunoelectrophoresis for multiple myeloma. Genetic testing is also increasingly available and useful. Patients with a family history of CKD, early onset of CKD, syndromic features, or cystic or congenital abnormalities may harbor genetic causes of CKD that, in some cases, inform prognosis or treatment plans (24). For example, *APOL1* risk variants are relatively common in African American populations and lead to higher risk for kidney failure. Testing for *APOL1* may help personalize treatment plans, particularly in patients with African ancestry, albuminuria, and no history of diabetes.

How should physicians talk to their patients about CKD?

Many people with CKD are not aware of their diagnosis, and those who are aware often report wishing they had known earlier (26). Thus, screening for and discussing CKD is imperative from both a treatment perspective and a patient-centered perspective. Discussions should include education on the basic components of kidney damage, function, and risk as well as risk for other associated conditions. Albuminuria indicates kidney damage, with higher values posing higher risk for kidney disease progression and cardiovascular disease. Importantly, albuminuria is modifiable, and thus patients with albuminuria should be prescribed medications that decrease it, such as angiotensin-converting enzyme (ACE)

26. Chu L, Bhogal SK, Lin P, et al. AWAREness of Diagnosis and Treatment of Chronic Kidney Disease in Adults With Type 2 Diabetes (AWARE-CKD in T2D). Can J Diabetes. 2022;46:464-472. [PMID: 35739044]

Downloaded from https://annals.org by Universidad Nacional Autonoma on 09/12/2025.

Table 2. **Examples of Medications That Require Dose Adjustment in CKD***

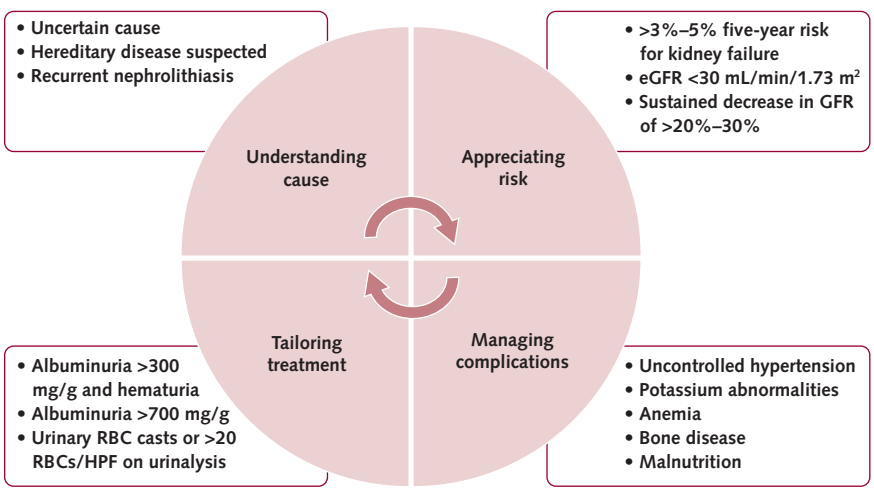
Type	*Examples*
Antibiotics	Aminoglycosides, aztreonam, cephalosporins, clarithromycin, fluoroquinolones, imipenem, meropenem, nitrofurantoin, penicillins, sulfonamides, vancomycin
Anticoagulants	Direct oral anticoagulants, enoxaparin
Antiepileptics	Gabapentin, topiramate
Antifungals	Fluconazole
Antigout	Allopurinol, colchicine
Antihistamines	Famotidine, ranitidine, cetirizine, loratadine
Antivirals	Acyclovir, foscarnet, ganciclovir, lamivudine
Chemotherapy	Methotrexate, platinum-based compounds, ifosfamide, cyclophosphamide, etoposide, topotecan, capecitabine, pemetrexed, fludarabine, bleomycin, gemcitabine, lenalidomide, bortezomib
Lipid medications	Fenofibrate, rosuvastatin
Diabetes medications	Metformin, glyburide, glimepiride, canagliflozin, dapagliflozin, empagliflozin, exenatide, sitagliptin, saxagliptin, alogliptin
Muscle relaxants	Baclofen
Pain medications	Morphine, pregabalin
Other medications	Lithium, metoclopramide

CKD = chronic kidney disease.
** Adapted from reference 77.*

inhibitors and angiotensin-receptor blockers (ARBs), SGLT-2 inhibitors, GLP-1RAs, and nonsteroidal mineralocorticoid receptor antagonists (nsMRAs). eGFR should be explained as the central estimate of kidney function which is typically based on serum creatinine and/or cystatin C. A person's eGFR must be considered in medication dosing (Table 2). Risks of CKD include not only kidney failure but also cardiovascular disease, infection, and CKD-related bone disorders and fractures.

Counseling patients about absolute risks or the chance of developing complications of CKD can be helpful in framing discussions. The Kidney Failure Risk Equation (KFRE; https://kidneyfailurerisk.com) provides 2- and 5-year risks for kidney failure based on 4 or 8 readily available clinical variables for people with eGFR below 60 mL/min/1.73 m^2 (27). Estimates from the KFRE can be leveraged in discussions between physicians and patients to discuss the patient's risk

Figure 2. **Reasons for nephrology referral.**



Adapted from reference 2. eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; HPF = high-power field; RBC = red blood cell.

27. Tangri N, Grams ME, Levey AS, et al; CKD Prognosis Consortium. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. JAMA. 2016;315:164-174. [PMID: 26757465]
28. Khan SS, Matsushita K, Sang Y, et al; Chronic Kidney Disease Prognosis Consortium and the American Heart Association Cardiovascular-Kidney-Metabolic Science Advisory Group. Development and validation of the American Heart Association's PREVENT equations. Circulation. 2024;149:430-449. [PMID: 37947085]
29. Grams ME, Sang Y, Ballew SH, et al. Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate. Kidney Int. 2018;93:1442-1451. [PMID: 29605094]
30. Liu P, Sawhney S, Heide-Jørgensen U, et al. Predicting the risks of kidney failure and death in adults with moderate to severe chronic kidney disease: multinational, longitudinal, population based, cohort study. BMJ. 2024;385:e078063. [PMID: 38621801]

 © 2025 American College of Physicians

Downloaded from https://annals.org by Universidad Nacional Autonoma on 09/12/2025.

31. Hingwala J, Wojciechowski P, Hiebert B, et al. Risk-based triage for nephrology referrals using the Kidney Failure Risk Equation. Can J Kidney Health Dis. 2017;4:2054358117722-782. [PMID: 28835850]
32. Agarwal R, Fouque D. The foundation and the four pillars of treatment for cardiorenal protection in people with chronic kidney disease and type 2 diabetes. Nephrol Dial Transplant. 2023;38:253-257. [PMID: 36535638]
33. Fried LF, Emanuele N, Zhang JH, et al; VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med. 2013;369:1892-1903. [PMID: 24206457]
34. Mann JFE, Schmieder RE, McQueen M, et al; ONTARGET investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet. 2008;372:547-553. [PMID: 18707986]
35. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med. 1993;329:1456-1462. [PMID: 8413456]
36. Lewis EJ, Hunsicker LG, Clarke WR, et al; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345:851-860. [PMID: 11565517]
37. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383:1436-1446. [PMID: 32970396]
38. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644-657. [PMID: 28605608]
39. Perkovic V, Jardine MJ, Neal B, et al; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380:2295-2306. [PMID: 30990260]

for progression—often for reassurance, particularly among older people with minimal albuminuria—and make appropriate referrals, including to a nephrologist or for vascular access or transplant. These risk-based discussions are recommended in the NICE guidelines from the United Kingdom, which suggest discussing a patient's 5-year risk for needing kidney replacement therapy with the patient and family, with documentation of the discussion and any decisions that are made (4). Other useful risk tools include those estimating cardiovascular disease, such as AHA's PREVENT (Predicting Risk of cardiovascular disease EVENTs) calculator (28). Holistic calculators that simultaneously estimate risks for kidney failure, cardiovascular disease, and all-cause mortality are also useful in patients with advanced CKD (29, 30).

When should clinicians consider consulting with a nephrologist?

KDIGO guidelines recommend referral to a nephrologist when kidney failure risk exceeds 3% to 5% over 5 years (4, 30, 31). Other indications for a nephrology consultation include eGFR below 30 mL/min/1.73 m^2, rapid decrease in kidney function (>5 mL/min/1.73 m^2 per year), unclear cause of CKD, persistent stage A3 albuminuria (ACR ≥300 mg/g), or sustained hematuria (**Figure 2**). Patients with suspected glomerulonephritis should be referred urgently because kidney biopsy may be required for a definitive diagnosis and rapid initiation of immunosuppressive therapies may help to reverse disease.

Diagnosis... CKD is defined as persistent albuminuria above 30 mg/g, GFR below 60 mL/min/1.73 m^2, or other stigmata of kidney damage. CKD should be staged based on levels of GFR and albuminuria and, when possible, cause. The history and physical examination often point to a cause, but a definitive diagnosis requires various diagnostic tests, kidney ultrasonography, and sometimes kidney biopsy. It is critical to discuss the diagnosis of CKD with the patient once it is identified.

CLINICAL BOTTOM LINE

Treatment

What are the pillars of management in CKD?

There are now many effective therapies that not only slow CKD progression but also prevent cardiovascular complications, leading to the concept of "pillars of management" in CKD (32). In patients with CKD and type 2 diabetes, these include 4 classes of medications: ACE inhibitors or ARBs, SGLT-2 inhibitors, GLP-1RAs, and nsMRAs.

ACE inhibitors or ARBs

For most patients with CKD, either an ACE inhibitor or an ARB is recommended. These medications forestall CKD progression in people with and without diabetes. KDIGO and ADA guidelines suggest that ACE inhibitors or ARBs should be prescribed to patients with CKD and hypertension who have urine albumin excretion above 300 mg/d and those with diabetes who have urine albumin excretion above 30 mg/d, even in the absence of hypertension (2, 3). Combination therapy with an ACE inhibitor and an ARB is not recommended in patients with CKD due to increased risk for adverse kidney events and hyperkalemia (33, 34). Because ACE inhibitors and ARBs also have protective effects on cardiovascular disease and mortality, cardiovascular guidelines, such as the 2017 American College of Cardiology (ACC)/AHA guideline, recommend adding ACE inhibitors or ARBs in any patient with CKD and hypertension, regardless of albuminuria levels (11).

Downloaded from https://annals.org by Universidad Nacional Autonoma on 09/12/2025.

In a trial of patients with diabetic nephropathy, 207 patients received captopril and 202 received placebo. Over a median follow-up of 2.5 years, serum creatinine concentrations doubled in 25 patients in the captopril group compared with 43 in the placebo group (43% reduction [CI, 6% to 65%]). Captopril treatment reduced risk for the combined end point of death, dialysis, and transplant by 50% (35).

The IDNT trial was a randomized, double-blind, placebo-controlled study that compared irbesartan with amlodipine or placebo in hypertensive patients with type 2 diabetes. Compared with amlodipine, irbesartan reduced risk for a composite outcome of doubling of serum creatinine levels, end-stage kidney disease (ESKD), or death by 23% (relative risk, 0.77 [CI, 0.63 to 0.93]). Compared with placebo, irbesartan reduced risk for the composite outcome by 20% (relative risk, 0.80 [CI, 0.66 to 0.97]); it also reduced proteinuria more than amlodipine and placebo (36).

SGLT-2 inhibitors

SGLT-2 inhibitors, such as empagliflozin, canagliflozin, and dapagliflozin, were originally developed as oral hypoglycemic medications but are now recognized as one of the most effective therapies for patients with CKD. They have been shown to decrease CKD progression in both diabetic and nondiabetic kidney disease as well as reducing the incidence of cardiovascular events and all-cause mortality (37–39). KDIGO guidelines recommend using an SGLT-2 inhibitor in all eligible patients with CKD and type 2 diabetes and all patients with urine ACR above 200 mg/g even in the absence of diabetes (2). SGLT-2 inhibitors are also recommended for patients with CKD and heart failure regardless of diabetes status, given their efficacy in reducing heart failure hospitalization.

The CREDENCE trial randomly assigned 4401 patients with eGFR of 30 to less than 90 mL/min/1.73 m^2 and albuminuria above 300 mg/g on renin–angiotensin blockade to canagliflozin, 100 mg/d, or placebo. The primary outcome was a composite of kidney failure, a doubling of serum creatinine level, or death due to renal or cardiovascular causes. Participants randomly assigned to canagliflozin had fewer primary outcomes than those receiving placebo (HR, 0.70 [CI, 0.59 to 0.82]) (39).

The EMPA-KIDNEY trial randomly assigned 6609 participants with eGFR of 20 to 45 mL/min/1.73 m^2 regardless of albuminuria or eGFR of 45 to 90 mL/min/1.73 m^2 with albuminuria above 200 mg/g to either empagliflozin, 10 mg/d, or placebo. Participants randomly assigned to empagliflozin experienced fewer events of a composite of progression of kidney disease or cardiovascular disease death (HR, 0.72 [CI, 0.64 to 0.82]) (40). Risk for hospitalization was also lower in the empagliflozin group (38).

The DAPA-CKD trial randomly assigned 4304 participants with eGFR of 25 to 75 mL/min/1.73 m^2 and albuminuria above 200 mg/g to either dapagliflozin, 10 mg, or placebo. Participants randomly assigned to dapagliflozin experienced fewer events of a composite of kidney disease progression or death due to kidney or cardiovascular causes (HR, 0.61 [CI, 0.51 to 0.72]) (37).

GLP-1RAs

GLP-1RAs are another class of medications initially developed for type 2 diabetes before evidence emerged supporting their wide-ranging utility in forestalling CKD progression, preventing cardiovascular events, and reducing weight. KDIGO guidelines recommend GLP-1RAs for people with type 2 diabetes who have residual albuminuria or need additional glycemic control (2). Recent evidence from the FLOW and SELECT trials has further increased interest in GLP-1RAs (10, 41, 42).

The FLOW trial randomly assigned 3533 participants with type 2 diabetes and urine ACR above 300 mg/g if eGFR was between 50 and 75 mL/min/1.73 m^2

40. Herrington WG, Staplin N, Wanner C, et al; The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. N Engl J Med. 2023;388:117-127. [PMID: 36331190]
41. Perkovic V, Tuttle KR, Rossing P, et al; FLOW Trial Committees and Investigators. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med. 2024;391:109-121. [PMID: 38785209]
42. Mann JFE, Rossing P, Bakris G, et al. Effects of semaglutide with and without concomitant SGLT2 inhibitor use in participants with type 2 diabetes and chronic kidney disease in the FLOW trial. Nat Med. 2024;30:2849-2856. [PMID: 38914124]
43. Bakris GL, Agarwal R, Chan JC, et al; Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) Study Group. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. JAMA. 2015;314:884-894. [PMID: 26325557]
44. Pitt B, Kober L, Ponikowski P, et al. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. Eur Heart J. 2013;34:2453-2463. [PMID: 23713082]
45. Bakris GL, Agarwal R, Anker SD, et al; FIDELIO-DKD Investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383:2219-2229. [PMID: 33264825]
46. Pitt B, Filippatos G, Agarwal R, et al; FIGARO-DKD Investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med. 2021;385:2252-2263. [PMID: 34449181]
47. Cheung AK, Chang TI, Cushman WC, et al. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int. 2021;99:S1-S87. [PMID: 33637192]

 © 2025 American College of Physicians

Downloaded from https://annals.org by Universidad Nacional Autonoma on 09/12/2025.

or urine ACR above 100 mg/g if eGFR was between 25 and less than 50 mL/min/1.73 m^2 to either semaglutide or placebo. The risk for the primary outcome (a composite of kidney failure, >50% reduction in eGFR from baseline, or death due to kidney- or cardiovascular-related causes) was 24% lower in the semaglutide group (HR, 0.76 [CI, 0.66 to 0.88]). A subsequent post hoc analysis suggested there was no statistical difference in the efficacy of semaglutide among people with or without concurrent SGLT-2 inhibitor use (41, 42).

Finerenone

Finerenone is an nsMRA that causes less hyperkalemia than steroidal MRAs used in heart failure (43, 44). Two large randomized clinical trials suggest that finerenone improves kidney and cardiovascular outcomes in patients with kidney disease and type 2 diabetes (45). Ongoing studies are evaluating finerenone in nondiabetic kidney disease (ClinicalTrials.gov: NCT05047263). KDIGO guidelines suggest finerenone use in patients with diabetes and residual urine ACR over 30 mg/g who are already receiving ACE inhibitor or ARB therapy.

The FIDELIO-DKD trial randomly assigned 5734 participants to receive finerenone or placebo. Eligible patients had diabetic retinopathy, urine ACR between 30 and 300 mg/g and eGFR between 25 and less than 60 mL/min/1.73 m^2, or urine ACR above 300 mg/g with an eGFR between 25 and less than 75 mL/min/1.73 m^2. There was an 18% reduction in the primary end point, a composite of kidney failure, 50% decrease in eGFR, or death due to renal causes (HR, 0.82 [CI, 0.73 to 0.93]; P = 0.001), with a similar reduction in cardiovascular events (45).

The FIGARO-DKD trial randomly assigned 7437 participants to receive finerenone or placebo. Eligible patients had urine ACR between 30 and 300 mg/g and eGFR between 25 and less than 90 mL/min/1.73 m^2 or urine ACR above 300 mg/g with an eGFR of 60 mL/min/1.73 m^2 or higher. The primary outcome was a composite of death due to cardiovascular causes, nonfatal myocardial infarction, stroke, or heart failure. The secondary outcome was a composite of kidney failure, 40% decrease in eGFR, or death due to renal causes. There was a 13% reduction in the primary end point (HR, 0.87 [CI, 0.76 to 0.98]), with a reduction in kidney events that was similar in effect size but not statistically significant (46).

What is the role of blood pressure management?

Patients with CKD are at high risk for cardiovascular disease, and treatment of hypertension reduces this risk. KDIGO guidelines recommend that patients with CKD and hypertension should be treated to a systolic blood pressure goal of less than 120 mm Hg (47). In kidney transplant recipients, the goal blood pressure is less than 130/80 mm Hg. These recommendations are based not on the efficacy of intensive blood pressure control in preventing kidney failure but instead its efficacy in preventing cardiovascular events and mortality. Recommendations were driven by results from the SPRINT trial, which showed a 27% lower risk for cardiovascular events and mortality with an intensive blood pressure control regimen (12). Patients often need at least 3 medications, including a diuretic, to achieve systolic blood pressure below 120 mm Hg.

What is the role of glycemic control in patients with diabetes and CKD?

Diabetes is the most common cause of ESKD in the United States (1). Poor glycemic control is associated with development and progression of diabetic nephropathy, and evidence suggests that glycemic control may forestall the development of albuminuria and other microvascular complications (48). The major trials in glycemic control—including the U.K. Prospective Diabetes Study, the ACCORD trial, the ADVANCE trial, and the Veterans Affairs Diabetes Trial—were conducted before the introduction of GLP-1RAs and SGLT-2 inhibitors,

48. Ruospo M, Saglimbene VM, Palmer SC, et al. Glucose targets for preventing diabetic kidney disease and its progression. Cochrane Database Syst Rev. 2017;6: Cd010137. [PMID: 28594069]
49. Gerstein HC, Miller ME, Byington RP, et al; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545-2559. [PMID: 18539917]
50. Patel A, MacMahon S, Chalmers J, et al; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358: 2560-2572. [PMID: 18539916]
51. Duckworth WC, McCarren M, Abraira C; VA Diabetes Trial. Glucose control and cardiovascular complications: the VA Diabetes Trial. Diabetes Care. 2001;24:942-945. [PMID: 11347758]
52. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:854-865. [PMID: 9742977]
53. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. 2022;102:S1-S127. [PMID: 36272764]
54. Ikizler TA, Kramer HJ, Beddhu S, et al; ASN Kidney Health Guidance Workgroup on Obesity and Kidney Diseases. ASN kidney health guidance on the management of obesity in persons living with kidney diseases. J Am Soc Nephrol. 2024;35:1574-1588. [PMID: 39292519]
55. Ndumele CE, Neeland IJ, Tuttle KR, et al; American Heart Association. A synopsis of the evidence for the science and clinical management of cardiovascular-kidney-metabolic (CKM) syndrome: a scientific statement from the American Heart Association. Circulation. 2023;148:1636-1664. [PMID: 37807920]

Downloaded from https://annals.org by Universidad Nacional Autonoma on 09/12/2025.

which have demonstrated efficacy in preventing cardiovascular and kidney events (49–52). Because CKD increases risk for hypoglycemia and data on intensive glycemic control are mixed (for example, the ACCORD trial was stopped early because of a mortality signal), both the ADA and the KDIGO guidelines emphasize the importance of a more nuanced approach to a target hemoglobin A_{1c} (HbA_{1c}) level (3, 53). Although the ADA suggests that a target HbA_{1c} level below 7% can be appropriate for many nonpregnant adults, it also states that less stringent HbA_{1c} goals may be appropriate for patients with limited life expectancy or specific comorbidities. The KDIGO guidelines suggest individualized glycemic targets incorporating patient comorbidities and preferences, with a broad range of targets from less than 6.5% to less than 8%.

What nondrug therapies should clinicians recommend?

Lifestyle and dietary modifications may improve outcomes for specific types of CKD. General cardiovascular, kidney, and metabolic health recommendations apply to all patients with CKD: abstain from smoking; exercise for 30 minutes most days of the week; maintain body mass index within the normal range (18.5 to 24.9 kg/m^2); and eat a diet high in fruit, vegetables, and whole grains, such as the DASH (Dietary Approaches to Stop Hypertension) diet (34, 35, 54, 55). Salt restriction to less than 2.0 g/d is recommended by the KDIGO guidelines given possible effects on hypertension and albuminuria incidence (2). Although evidence is weak, some suggest that patients with CKD should avoid high-protein diets (>1.3 g/kg/d); KDIGO recommends a target of 0.8 g/kg/d. Given the risk for infection, guidelines also recommend routine vaccination for patients with CKD, including the pneumococcal vaccine (56).

How should clinicians treat cardiovascular risk factors?

Cardiovascular disease is the most common adverse outcome in patients with CKD (57). Besides promoting lifestyle measures and treating hypertension and diabetes, KDIGO guidelines recommend treatment with a statin or a statin–ezetimibe combination regardless of cholesterol level among adults aged 50 years or older with CKD (58, 59). Rosuvastatin may require renal adjustment (**Table 2**), and the maximum dose is 10 mg in patients with GFR below 30 mL/min/1.73 m^2. Low-dose aspirin is also recommended for people with ischemic cardiovascular disease and CKD for prevention of recurrent cardiovascular events.

In the randomized, double-blind SHARP trial, 4650 patients with CKD were assigned to simvastatin, 20 mg/d, plus ezetimibe, 10 mg/d, and 4620 were assigned to placebo. Major atherosclerotic events were reduced by 17% (CI, 6% to 26%) in the simvastatin–ezetimibe group. However, no differences were noted in rates of nonfatal myocardial infarction or death due to coronary heart disease (58).

How should clinicians manage metabolic complications?

Patients with CKD develop metabolic abnormalities as glomerular filtration and the kidneys' ability to synthesize hormones decrease. The main metabolic complications of concern are hyperkalemia, metabolic acidosis, and CKD–mineral and bone disorder (CKD-MBD).

Hyperkalemia

Hyperkalemia is a late manifestation of CKD and is more common in patients with diabetes (60). Specific kidney-protective medications, such as ACE inhibitors, ARBs, and MRAs, can also increase potassium levels. Elevated potassium levels can be treated with specific potassium binders, such as patiromer or sodium zirconium cyclosilicate. Concomitant patiromer use has been shown to help optimize adherence to guideline-directed management in heart failure, enabling higher doses of MRAs and fewer hyperkalemia events (61). Other guideline-recommended therapies

56. Kobayashi M, Leidner AJ, Gierke R, et al. Expanded recommendations for use of pneumococcal conjugate vaccines among adults aged ≥50 years: recommendations of the Advisory Committee on Immunization Practices - United States, 2024. MMWR Morb Mortal Wkly Rep. 2025;74:1-8. [PMID: 39773952]
57. Grams ME, Coresh J, Matsushita K, et al; Writing Group for the CKD Prognosis Consortium. Estimated glomerular filtration rate, albuminuria, and adverse outcomes: an individual-participant data meta-analysis. JAMA. 2023;330:1266-1277. [PMID: 37787795]
58. Baigent C, Landray MJ, Reith C, et al; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377:2181-2192. [PMID: 21663949]
59. Tonelli M, Wanner C; Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. Lipid management in chronic kidney disease: synopsis of the Kidney Disease: Improving Global Outcomes 2013 clinical practice guideline. Ann Intern Med. 2014;160:182. [PMID: 24323134]
60. Kovesdy CP, Matsushita K, Sang Y, et al; CKD Prognosis Consortium. Serum potassium and adverse outcomes across the range of kidney function: a CKD Prognosis Consortium meta-analysis. Eur Heart J. 2018;39:1535-1542. [PMID: 29554312]
61. Butler J, Anker SD, Lund LH, et al. Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: the DIAMOND trial. Eur Heart J. 2022;43:4362-4373. [PMID: 35900838]

 © 2025 American College of Physicians

Downloaded from https://annals.org by Universidad Nacional Autonoma on 09/12/2025.

may also improve adherence. For example, SGLT-2 inhibitors result in lower risk for hyperkalemia and fewer discontinuations of renin–angiotensin–aldosterone system blockade (62). Treatment of metabolic acidosis can also lead to fewer episodes of hyperkalemia (63).

Metabolic acidosis

CKD-associated metabolic acidosis is rare until GFR decreases below 30 mL/min/1.73 m^2 (64). Chronic metabolic acidosis is associated with progression of CKD, insulin resistance, muscle dysfunction, and altered bone metabolism. Clinical trials have not shown slower progression in patients treated with alkali therapy. Current guidelines recommend alkali therapy for patients with CKD with serum bicarbonate level below 18 mmol/L (2).

CKDMBD

CKD-MBD encompasses a wide range of abnormalities that are present with advancing CKD, including renal osteodystrophy, vascular calcification, elevated phosphate and intact PTH levels, and low calcium and 1,25-dihydroxyvitamin D levels. Derangements in CKD-MBD biomarkers are usually most pronounced after the GFR falls below 30 mL/min/1.73 m^2 (64, 65). Hyperphosphatemia and 1,25-dihydroxyvitamin D deficiency cause hypocalcemia. Hyperphosphatemia, 1,25-dihydroxyvitamin D deficiency, and hypocalcemia induce secondary hyperparathyroidism. Current recommendations suggest serial assessments of calcium, phosphate, and intact PTH levels. Although no high-quality studies have shown a long-term benefit, guidelines suggest a combination of dietary phosphorus restriction, phosphate binders, and vitamin D supplementation, with the goals of maintaining serum calcium and phosphorus within the normal ranges, treating patients with elevated intact PTH levels, and correcting 25-hydroxyvitamin D (calcidiol) deficiency and insufficiency (66). Osteoporosis is common in CKD and leads to a higher risk for fracture in patients with CKD compared with the general population (67). Patients who are at risk for osteoporosis should be screened and treated.

How should clinicians manage patients with anemia?

Anemia is more common with lower eGFR and higher urine ACR (68). Anemia is associated with several poor outcomes, including decreased quality of life, left ventricular hypertrophy, and cardiovascular complications in patients with CKD (68–71). Although patients with normocytic, normochromic anemia and a low reticulocyte count are likely to have anemia of chronic disease, all anemia should be evaluated for reversible causes. This evaluation of patients with CKD and anemia should include complete blood count, reticulocyte count, transferrin saturation (TSAT), and ferritin level. Iron deficiency in patients not receiving dialysis has been suggested as ferritin level below 100 μg/L and TSAT below 40% or ferritin level below 300 μg/L and TSAT below 25%. Patients with iron deficiency should be evaluated to identify potential sources of bleeding and should initiate iron therapy (72). KDIGO guidelines recommend using intravenous iron for patients receiving hemodialysis and oral or intravenous therapy for people with CKD not receiving hemodialysis.

Once all reversible causes of anemia have been addressed (such as infection, inflammation, hypothyroidism, hyperparathyroidism, cancer, blood loss, malnutrition, iron deficiency, vitamin B_{12} or folate deficiency, bone marrow dysfunction, or hemolysis), a subcutaneous or intravenous erythropoietin-stimulating agent (ESA) or an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (approved in patients receiving dialysis for ≥4 months) could be considered, weighing the potential benefit to patient symptoms against the risk for adverse events, which include cancer, stroke, and cardiovascular events. Hemoglobin should not be "normalized" but should be maintained at a level below 11.5 g/dL (72). Targeting higher hemoglobin levels (>13 g/dL) is associated with increased cardiovascular events (73). Patients with

62. Fletcher RA, Jongs N, Chertow GM, et al. Effect of SGLT2 inhibitors on discontinuation of renin-angiotensin system blockade: a joint analysis of the CREDENCE and DAPA-CKD trials. J Am Soc Nephrol. 2023;34:1965-1975. [PMID: 37876229]
63. Melamed ML, Horwitz EJ, Dobre MA, et al. Effects of sodium bicarbonate in CKD stages 3 and 4: a randomized, placebo-controlled, multicenter clinical trial. Am J Kidney Dis. 2020;75:225-234. [PMID: 31699517]
64. Inker LA, Grams ME, Levey AS, et al; CKD Prognosis Consortium. Relationship of estimated GFR and albuminuria to concurrent laboratory abnormalities: an individual participant data meta-analysis in a global consortium. Am J Kidney Dis. 2019;73:206-217. [PMID: 30348535]
65. Levin A, Bakris GL, Molitch M, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the Study to Evaluate Early Kidney Disease. Kidney Int. 2007;71:31-38. [PMID: 17091124]
66. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl (2011). 2017;7:1-59. [PMID: 30675420]
67. Nickolas TL, McMahon DJ, Shane E. Relationship between moderate to severe kidney disease and hip fracture in the United States. J Am Soc Nephrol. 2006;17:3223-3232. [PMID: 17005938]
68. Farrington DK, Sang Y, Grams ME, et al. Anemia prevalence, type, and associated risks in a cohort of 5.0 million insured patients in the United States by level of kidney function. Am J Kidney Dis. 2023;81:201-209.e1. [PMID: 36181996]
69. He J, Shlipak M, Anderson A, et al; CRIC (Chronic Renal Insufficiency Cohort) Investigators. Risk factors for heart failure in patients with chronic kidney disease: the CRIC (Chronic Renal Insufficiency Cohort) study. J Am Heart Assoc. 2017;6:e005336. [PMID: 28515118]

Downloaded from https://annals.org by Universidad Nacional Autonoma on 09/12/2025.

active cancer or a history of stroke should be considered to be at high risk for adverse events associated with ESA therapy.

In the TREAT trial, 4038 patients with diabetes, CKD, and anemia were randomly assigned to darbepoetin-α and a target hemoglobin level of 13 g/dL versus placebo with rescue darbepoetin-α when hemoglobin levels dropped below 9 g/dL. There was no difference in the rate of death or cardiovascular events between groups. Although both groups reported improvement in the FACT-Fatigue score from baseline to 25 weeks, the improvement was greater in the darbepoetin-α group. However, compared with the placebo group, the group that received darbepoetin-α had an HR for fatal or nonfatal stroke of 1.92 (CI, 1.38 to 2.68) (74).

The PIVOTAL trial randomly assigned 2141 participants receiving maintenance hemodialysis to either proactive intravenous iron sucrose, 400 mg monthly, or as-needed iron sucrose, administered intravenously when ferritin level was below 200 μg/L or TSAT was below 20%. The primary end point was fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure. Proactive iron sucrose therapy resulted in an improvement in the primary end point (HR, 0.80 [CI, 0.64 to 1.00]) (75).

How should clinicians monitor patients with CKD?

Clinicians should monitor for progression of CKD and its complications regularly, with frequency of monitoring guided by disease severity (2) (**Figure 1**). People with severely increased albuminuria (≥300 mg/g) and those with severely decreased eGFR (<30 mL/min/1.73 m^2) should have eGFR and albuminuria tested 3 to 4 times per year. Patients with less severe CKD should generally be followed at least annually, and more frequently if needed for medication monitoring or other concomitant disease. All clinical visits to evaluate kidney function should also assess blood pressure. Patients should be referred for nephrology evaluation when the cause of CKD is uncertain, when a hereditary kidney disease is suspected, when the risk for kidney failure exceeds 3% to 5% (as estimated using an equation such as the KFRE), when eGFR is below 30 mL/min/1.73 m^2, when albuminuria is above 700 mg/g, when both albuminuria and hematuria are present, or when albuminuria is increasing. Nephrologists can also help manage CKD complications, including hypertension (**Figure 2**), and discuss options for renal replacement versus palliative care.

What are the indications for renal replacement therapy?

Common indications to initiate dialysis are volume overload that is unresponsive to diuretics and progressive "uremic" symptoms, such as fatigue, nausea and vomiting, loss of appetite, dysgeusia, evidence of malnutrition, and insomnia. Pericarditis, uremic encephalopathy, hyperkalemia, and metabolic acidosis that cannot be managed medically are less common indications for initiation of renal replacement therapy. A nephrologist can discuss treatment options for ESKD, which may include hemodialysis, peritoneal dialysis, or kidney transplant; provide counseling, psychoeducational interventions, and referral for fistula placement or transplant evaluation; and initiate dialysis when appropriate (12). With appropriate CKD management and timely referrals, patients with CKD can often avoid hospitalization and initiate dialysis in the outpatient setting or receive a preemptive kidney transplant. Some patients may prefer not to initiate renal replacement therapy, opting instead for conservative kidney management, which is generally directed by a nephrologist in combination with a palliative care specialist. Although no randomized controlled trials have tested conservative kidney management, some observational studies suggest that, for older patients with multiple comorbid conditions who are not transplant candidates, conservative kidney management may achieve better quality of life and similar survival compared with initiation of renal replacement therapy (76).

70. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol. 2001;38:955-962. [PMID: 11583864]
71. Kovesdy CP, Trivedi BK, Kalantar-Zadeh K, et al. Association of anemia with outcomes in men with moderate and severe chronic kidney disease. Kidney Int. 2006;69:560-564. [PMID: 16395253]
72. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2025 Clinical Practice Guideline for Anemia in Chronic Kidney Disease (CKD): Public Review Draft. November 2024.
73. Singh AK, Szczech L, Tang KL, et al; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355:2085-2098. [PMID: 17108343]
74. Pfeffer MA, Burdmann EA, Chen C-Y, et al; TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361:2019-2032. [PMID: 19880844]
75. Macdougall IC, White C, Anker SD, et al; PIVOTAL Investigators and Committees. Intravenous iron in patients undergoing maintenance hemodialysis. N Engl J Med. 2019;380:447-458. [PMID: 30365356]
76. Montez-Rath ME, Thomas IC, Charu V, et al. Effect of starting dialysis versus continuing medical management on survival and home time in older adults with kidney failure: a target trial emulation study. Ann Intern Med. 2024;177:1233-1243. [PMID: 39159459]
77. Hassan Y, Al-Ramahi R, Abd Aziz N, et al. Drug use and dosing in chronic kidney disease. Ann Acad Med Singap. 2009;38:1095-1103. [PMID: 20052447]
78. Haines RW, Fowler AJ, Liang K, et al. Comparison of cystatin C and creatinine in the assessment of measured kidney function during critical illness. Clin J Am Soc Nephrol. 2023;18:997-1005. [PMID: 37256861]

 © 2025 American College of Physicians

Downloaded from https://annals.org by Universidad Nacional Autonoma on 09/12/2025.

How should patients with CKD be cared for in the hospital setting?

Patients with CKD require special care in the hospital setting for several reasons. First, many inpatient medications are cleared by the kidney, and dosing adjustments are frequently necessary. Notable medications that require dose adjustments include direct oral anticoagulants; gabapentin; baclofen; and several antibiotics, including vancomycin, fluroquinolones, and cefepime (**Table 2**) (77). Second, patients with CKD are much more likely to have acute kidney injury than those with normal kidney function. Known nephrotoxic medications, such as aminoglycoside antibiotics, amphotericin B, and nonsteroidal anti-inflammatory drugs, should be avoided when possible. Third, changes in kidney function may not be as apparent in the hospital setting. Patients frequently lose muscle mass while hospitalized, which can result in inappropriately low serum creatinine concentrations for the level of kidney function (78).

In a small study of 38 patients receiving mechanical ventilation in the intensive care unit, the difference between eGFRcr and eGFRcys increased in proportion to muscle loss. By discharge, eGFRcr overestimated the gold standard–measured GFR by an estimated 59 mL/min/1.73 m^2, whereas eGFRcys overestimated measured GFR by 22 mL/min/1.73 m^2 (78).

Treatment... The main goals in treatment of CKD are to slow disease progression, prevent cardiovascular complications, and address associated metabolic abnormalities. Treatment of patients with CKD should align the risk for each of these outcomes with the therapeutic approach. Over the past decade, the pool of effective therapies has vastly increased and now includes not only ACE inhibitors and ARBs but also SGLT-2 inhibitors, nsMRAs, and GLP-1RAs. Guideline-directed management of patients with CKD slows the progression of kidney disease and prevents cardiovascular complications. Team-based care that incorporates specialists as well as primary care practitioners and incorporates shared decision making with the patient is the ideal approach to managing patients with CKD.

CLINICAL BOTTOM LINE

Downloaded from https://annals.org by Universidad Nacional Autonoma on 09/12/2025.

In the Clinic
Tool Kit

Chronic Kidney Disease

Patient Information

https://medlineplus.gov/chronickidneydisease.html
https://medlineplus.gov/languages/chronickidneydisease.html
Information on chronic kidney disease in English and other languages from the National Institutes of Health's MedlinePlus.

www.niddk.nih.gov/health-information/kidney-disease/chronic-kidney-disease-ckd
www.niddk.nih.gov/health-information/informacion-de-la-salud/enfermedades-rinones/informacion-general
Information on chronic kidney disease in English and Spanish from the National Institute of Diabetes and Digestive and Kidney Diseases.

www.kidney.org/kidney-topics/chronic-kidney-disease-ckd
www.kidney.org/es/kidney-topics/enfermedad-renal-cronica-erc
Information on chronic kidney disease in English and Spanish from the National Kidney Foundation.

Information for Health Professionals

www.kidney-international.org/article/S0085-2538(23)00766-4/fulltext
www.acpjournals.org/doi/10.7326/ANNALS-24-01926
KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease.

https://diabetesjournals.org/care/article/47/Supplement_1/S219/153938/11-Chronic-Kidney-Disease-and-Risk-Management
Information on chronic kidney disease and risk management from the ADA's *Standards of Care in Diabetes*.

www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease
Information on kidney disease for health professionals from the National Institute of Diabetes and Digestive and Kidney Diseases.

 © 2025 American College of Physicians

Downloaded from https://annals.org by Universidad Nacional Autonoma on 09/12/2025.

WHAT YOU SHOULD KNOW ABOUT CHRONIC KIDNEY DISEASE

What Is Chronic Kidney Disease?

The kidneys play an important role in keeping the body healthy. They remove waste from the body, balance blood pressure, make important hormones, and help keep bones strong. In chronic kidney disease (CKD), the kidneys gradually stop working. CKD can cause other health problems, such as:

- Heart disease
- Weak bones
- Nerve damage
- Fluid buildup
- Weakened immune system

CKD is most often caused by diabetes or high blood pressure, but other factors can cause the kidneys to stop working.

How Is It Diagnosed?

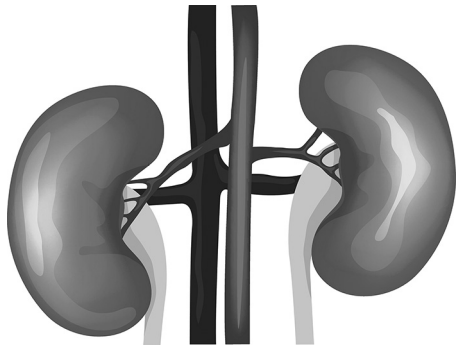
Many people with CKD do not notice symptoms until late in the disease. Your doctor will ask you about your family history and any other health problems you have, such as diabetes and high blood pressure.

Your doctor may also check your blood and urine. Blood tests can tell you how much blood your kidneys filter each minute. If your estimated glomerular filtration rate, or GFR, is less than 60 for 3 months or more, you might have CKD. Protein in your urine may suggest CKD is getting worse, and your doctor may suggest medications to slow the damage.

How Is It Treated?

Treating CKD early can prevent or slow down more damage to the kidneys or complications to the heart. Treatment can include:

- Taking medicines that help prevent further damage to the kidneys
- Controlling diabetes with diet and medications
- Controlling blood pressure with diet, exercise, and medications
- Avoiding cigarettes and drugs that may harm your kidneys
- Limiting salt intake
- Exercising regularly
- Maintaining a healthy body weight



Questions for My Doctor

- Am I at risk for or do I have kidney disease?
- How can I stop kidney disease from getting worse?
- Do I need medications to help keep my kidneys working longer?
- Is my diabetes and/or blood pressure under control?
- What is my risk for heart disease?
- Do I need to change my diet or alcohol intake?
- Can I still take the medicines I normally take?
- Will I ever need dialysis or a kidney transplant?

Bottom Line

- The kidneys are important for keeping the body healthy. In CKD, the kidneys gradually stop working.
- Symptoms of CKD are often not noticed until late in the disease.
- Tests of the blood and urine can help diagnose CKD.
- Treatment includes taking medicine, maintaining a healthy lifestyle, and managing the health problems that damage the kidneys.

For More Information

ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

National Kidney Foundation
www.kidney.org/kidneydisease/aboutckd

National Kidney Disease Education Program
www.nkdep.nih.gov

American Association of Kidney Patients
www.aakp.org

Patient Information

© 2025 American College of Physicians

Downloaded from https://annals.org by Universidad Nacional Autonoma on 09/12/2025.